

Applicants: Sharon Cohen-Vered et al.
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Amendments to the Claims

Please cancel claims 15, 17-23, 26, 28-35, 39-46 and 49-51 without prejudice or disclaimer to applicants' rights to pursue the subject matter of these claims in this or a related application.

Please amend claims 3, 5, 8-10, 12, 14, 16, 24, 27, 37, 38 and 48 under the provisions of 37 C.F.R. §1.121, as set forth in the Federal Register on June 30, 2003 as follows:

1. (Original) A pharmaceutical composition comprising:

an aqueous carrier;

from 0.1 mg/ml to 20 mg/ml of the composition of a pharmaceutically acceptable salt of

a) a peptide comprising at least 12 and at most 30 consecutive amino acids having a sequence corresponding to

(i) a sequence of amino acids found within a complementarity-determining region (CDR) of a heavy or a light chain of a human monoclonal anti-DNA 16/6 Id antibody, or

(ii) a sequence of amino acids found within a complementarity-determining region (CDR) of a heavy or a light chain of a pathogenic anti-DNA monoclonal antibody that induces a systemic lupus erythematosus (SLE)-like disease response in mice, or

b) a peptide comprising consecutive amino acids having the sequence

(i) TGYX₁X₂X₃X₄X₅QSPEKSLEWIG (SEQ ID NO:11)

wherein X₁ is Met, Ala or Val; X₂ is Gln, Asp, Glu or Arg; X₃ is Trp or Ala; X₄ is Val or Ser; and X₅ is Lys, Glu or Ala;

(ii) EINPSTGGX₆X₇X₈X₉X₁₀X₁₁X₁₂KAKAT (SEQ ID NO:12)

wherein X₆ and X₇ are each Thr, Val or Ala; X₈ is Tyr or Phe; X₉ is Asn or Asp; X₁₀ is Gln or Glu; X₁₁ is Lys or Glu, and X₁₂ is Phe or Tyr;

(iii) YYCARX₁₃X₁₄X₁₅X₁₆PYAX₁₇X₁₈YWGQGS (SEQ ID NO:13)

wherein X_{13} is Phe, Thr or Gly; X_{14} is Leu, Ala or Ser; X_{15} is Trp or Ala; X_{16} is Glu or Lys; X_{17} is Met or Ala, and X_{18} is Asp, Lys or Ser;

(iv) GYNX₁₉X₂₀X₂₁X₂₂X₂₃X₂₄SHGX₂₅X₂₆LEWIG (SEQ ID NO:14)

wherein X_{19} is Met or Ala; X_{20} is Asn, Asp or Arg; X_{21} is Trp or Ala; X_{22} is Val or Ser; X_{23} is Lys or Glu; X_{24} is Gln or Ala; X_{25} is Lys or Glu, and X_{26} is Ser or Ala;

(v) YYCARX₂₇X₂₈X₂₉YGX₃₀X₃₁X₃₂GQTL (SEQ ID NO:15)

wherein X_{27} is Ser or Phe; X_{28} is Gly or Ala; X_{29} is Arg, Ala or Glu; X_{30} is Asn or Asp; X_{31} is Tyr or Phe, and X_{32} is Trp, His or Ala;

(vi) X₃₃YYWSWIX₃₄QX₃₅PX₃₆X₃₇GX₃₈EWIG (SEQ ID NO:16)

wherein X_{33} is Gly or Thr Gly; X_{34} is Arg or Lys; X_{35} is Pro or Ser; X_{36} is Gly or Glu; X_{37} is Lys or Asp; and X_{38} is Glu, Leu or Ser;

(vii) YYCARX₃₉LLX₄₀X₄₁X₄₂X₄₃X₄₄DVDYX₄₅GX₄₆DV (SEQ ID NO:17)

wherein X_{39} is Gly or Phe; X_{40} is Arg or Ala; X_{41} is Gly or Ala; X_{42} is Gly or Ala; X_{43} is Trp or Ala; X_{44} is Asn or Ala; X_{45} is Tyr or Trp; X_{46} is Met or Gln;

(viii) FSGYYWS (SEQ ID NO:8);

(ix) EINHSGSTNYKTSLS (SEQ ID NO:9); or

(x) GLLRGGWNDVDYYYGMDV (SEQ ID NO:10), or

c) a peptide comprising consecutive amino acids having a sequence of any of a) and b), or at least two of the sequences in (a)(i), (a)(ii) and (b)(i) through (b)(x), or

d) a peptide comprising consecutive amino acids having a sequence comprising at least two identical sequences included in (a)(i), (a)(ii) and (b)(i)

through (b) (x); and

a solubility enhancer selected from the group consisting of dimethyl-acetamide, polyethylene glycol, polyoxylated castor oil, N-methyl-2-pyrrolidinone, 1-ethenyl-2-pyrrolidinone, polyoxyethylene sorbitan esters, and a substituted β -cyclodextrin,

wherein both the peptide and the solubility enhancer are dissolved in the aqueous carrier; and

wherein the composition has a pH between 4 and 9.

2. (Original) The pharmaceutical composition of claim 1, wherein at least 0.5 mg/ml of the composition is the pharmaceutically acceptable salt of the peptide.

3. (Currently Amended) The pharmaceutical composition of ~~claim 1 or 2~~, claim 1, wherein the peptide has a sequence selected from the group consisting of:

NH₂- Thr Gly Tyr Tyr Met Gln Trp Val Lys Gln Ser Pro Glu
Lys Ser Leu Glu-Trp Ile Gly-COOH (SEQ ID NO:1);

NH₂- Glu Ile Asn Pro Ser Thr Gly Gly Thr Thr Tyr Asn Gln
Lys Phe Lys Ala Lys Ala Thr-COOH (SEQ ID NO:2);

NH₂- Tyr Tyr Cys Ala Arg Phe Leu Trp Glu Pro Tyr Ala Met
Asp Tyr Trp Gly Gln Gly Ser-COOH (SEQ ID NO:3);

NH₂- Gly Tyr Asn Met Asn Trp Val Lys Gln Ser His Gly Lys
Ser Leu Glu Trp Ile Gly-COOH (SEQ ID NO:4);

NH₂- Tyr Tyr Cys Ala Arg Ser Gly Arg Tyr Gly Asn Tyr Trp
Gly Gln Thr Leu -COOH (SEQ ID NO:5);

NH₂-Gly Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
Glu Glu Trp Ile Gly-COOH (SEQ ID NO:6);

NH₂-Tyr Tyr Cys Ala Arg Gly Leu Leu Arg Gly Gly Trp Asn Asp
Val Asp Tyr Tyr Gly Met Asp Val-COOH (SEQ ID NO:7);
NH₂- Phe Ser Gly Tyr Tyr Trp Ser-COOH (SEQ ID NO:8);
NH₂- Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Lys Thr Ser
Leu Lys Ser-COOH (SEQ ID NO:9); and
NH₂- Gly Leu Leu Arg Gly Gly Trp Asn Asp Val Asp Tyr Tyr
Tyr Gly Met Asp Val-COOH (SEQ ID NO:10).

4. (Original) The pharmaceutical composition of claim 1, wherein the peptide comprises consecutive amino acids having the sequence

X₃₃YYWSWIX₃₄QX₃₅PX₃₆X₃₇GX₃₈EWIG (SEQ ID NO:16)

wherein X₃₃ is Gly or Thr Gly; X₃₄ is Arg or Lys;
X₃₅ is Pro or Ser; X₃₆ is Gly or Glu; X₃₇ is Lys
or Asp; and X₃₈ is Glu, Leu or Ser.

5. (Currently Amended) The pharmaceutical composition of ~~any one of claims 1-4~~, claim 1, wherein the solubility enhancer is a substituted β -cyclodextrin.
6. (Original) The pharmaceutical composition of claim 5, wherein the substituted β -cyclodextrin is a hydroxypropyl, a sulfobutyl ether, or asulfopropyl ether substituted β -cyclodextrin.
7. (Original) The pharmaceutical composition of claim 6, wherein the substituted β -cyclodextrin is a substituted sulfobutyl ether β -cyclodextrin.
8. (Currently Amended) The pharmaceutical composition of ~~any one of claims 1-7~~, claim 1, wherein the concentration of peptide in solution is at least 1 mg/ml.

9. (Currently Amended) The pharmaceutical composition of ~~any one of claims 1-7~~, claim 1, wherein the concentration of peptide in solution is at least 2.5 mg/ml.
10. (Currently Amended) The pharmaceutical composition of ~~any one of claims 1-9~~, claim 1, wherein the composition has a pH between 6.5 and 8.5.
11. (Original) The pharmaceutical composition of claim 10, wherein the composition has a pH between 7.5 and 8.5.
12. (Currently Amended) The pharmaceutical composition of ~~any one of claims 1-11~~, claim 1, wherein the pharmaceutically acceptable salt is an acetate salt.
13. (Original) The pharmaceutical composition of claim 5, wherein the pharmaceutically acceptable salt is an acetate salt, and the substituted β -cyclodextrin is hepta-(sulfobutyl ether)- β -cyclodextrin.
14. (Currently Amended) A method of alleviating symptoms of systemic lupus erythematosus (SLE) in a human subject comprising administering to the human subject the pharmaceutical composition of ~~any one of claims 1-13~~ claim 1 in an amount effective to alleviate the symptoms of the SLE in the human subject.
15. (Canceled)
16. (Currently Amended) A process for manufacturing the pharmaceutical composition of ~~any one of claims 1-13~~

claim 1, comprising the steps of:

- a) preparing a solution of dimethyl-acetamide, polyethylene glycol, polyoxylated castor oil, N-methyl-2-pyrrolidinone, 1-ethenyl-2-pyrrolidinone, polyoxyethylene sorbitan esters, or a substituted β -cyclodextrin in an aqueous carrier at a predetermined concentration;
- b) adding a predetermined amount of a pharmaceutically acceptable salt of
 - 1) a peptide comprising at least 12 and at most 30 consecutive amino acids having a sequence corresponding to
 - (i) a sequence of amino acids found within a complementarity-determining region (CDR) of a heavy or a light chain of a human monoclonal anti-DNA 16/6 Id antibody, or
 - (ii) a sequence of amino acids found within a complementarity-determining region (CDR) of a heavy or a light chain of a pathogenic anti-DNA monoclonal antibody that induces a systemic lupus erythematosus (SLE)-like disease response in mice,
 - 2) a peptide comprising amino acids having the sequence
 - (i) TGYX₁X₂X₃X₄X₅QSPEKSLEWIG (SEQ ID NO:11)
wherein X₁ is Met, Ala or Val; X₂ is Gln, Asp, Glu or Arg; X₃ is Trp or Ala; X₄ is Val or Ser; and X₅ is Lys, Glu or Ala;
 - (ii) EINPSTGGX₆X₇X₈X₉X₁₀X₁₁X₁₂KAKAT. (SEQ ID NO:12)

- wherein X_6 and X_7 are each Thr, Val or Ala; X_8 is Tyr or Phe; X_9 is Asn or Asp; X_{10} is Gln or Glu; X_{11} is Lys or Glu, and X_{12} is Phe or Tyr;
- (iii) $YYCARX_{13}X_{14}X_{15}X_{16}PYAX_{17}X_{18}YWGQGS$ (SEQ ID NO:13)
wherein X_{13} is Phe, Thr or Gly; X_{14} is Leu, Ala or Ser; X_{15} is Trp or Ala; X_{16} is Glu or Lys; X_{17} is Met or Ala, and X_{18} is Asp, Lys or Ser;
- (iv) $GYNX_{19}X_{20}X_{21}X_{22}X_{23}X_{24}SHGX_{25}X_{26}LEWIG$ (SEQ ID NO:14)
wherein X_{19} is Met or Ala; X_{20} is Asn, Asp or Arg; X_{21} is Trp or Ala; X_{22} is Val or Ser; X_{23} is Lys or Glu; X_{24} is Gln or Ala; X_{25} is Lys or Glu, and X_{26} is Ser or Ala;
- (v) $YYCARX_{27}X_{28}X_{29}YGX_{30}X_{31}X_{32}GQTL$ (SEQ ID NO:15)
wherein X_{27} is Ser or Phe; X_{28} is Gly or Ala; X_{29} is Arg, Ala or Glu; X_{30} is Asn or Asp; X_{31} is Tyr or Phe, and X_{32} is Trp, His or Ala;
- (vi) $X_{33}YYWSWIX_{34}QX_{35}PX_{36}X_{37}GX_{38}EWIG$ (SEQ ID NO:16)
wherein X_{33} is Gly or Thr Gly; X_{34} is Arg or Lys; X_{35} is Pro or Ser; X_{36} is Gly or Glu; X_{37} is Lys or Asp; and X_{38} is Glu, Leu or Ser;
- (vii) $YYCARX_{39}LLX_{40}X_{41}X_{42}X_{43}X_{44}DVDYX_{45}GX_{46}DV$ (SEQ ID NO:17)
wherein X_{39} is Gly or Phe; X_{40} is Arg or Ala; X_{41} is Gly or Ala; X_{42} is Gly or Ala; X_{43} is Trp or Ala; X_{44} is Asn or Ala; X_{45} is Tyr or Trp; X_{46} is Met or Gln;
- (viii) FSGYYWS (SEQ ID NO:8);
- (ix) EINHSGSTNYKTSLS (SEQ ID NO:9); or
- (x) GLLRGGWNDVDYYYGMDV (SEQ ID NO:10), or
- 3) a peptide comprising consecutive amino acids having a sequence of any of a) and b), or at least two of the sequences in (a)(i), (a)(ii) and (b)(i) through (b)(x), or

- 4) a peptide comprising consecutive amino acids having a sequence comprising at least two identical sequences included in (a)(i), (a)(ii) and (b)(i) through (b)(x);
- c) adjusting the pH of the solution of step b) until the peptide dissolves in the solution; and
- d) if necessary, adjusting the pH of the solution of step c) to a pH of 4-9, thereby manufacturing the pharmaceutical composition.

Claims 17-23. (Canceled)

- 24. (Currently Amended) A composition prepared by the process of ~~any one of claims 16-23~~ claim 16.
- 25. (Original) A lyophilized pharmaceutical composition comprising from 0.1 mg/ml to 20 mg/ml of the composition of a pharmaceutically acceptable salt of
 - a) a peptide comprising at least 12 and at most 30 consecutive amino acids having a sequence corresponding to
 - (i) a sequence of amino acids found within a complementarity-determining region (CDR) of a heavy or a light chain of a human monoclonal anti-DNA 16/6 Id antibody, or
 - (ii) a sequence of amino acids found within a complementarity-determining region (CDR) of a heavy or a light chain of a pathogenic anti-DNA monoclonal antibody that induces a systemic lupus erythematosus (SLE)-like disease response in mice, or
 - b) a peptide comprising consecutive amino acids having

the sequence

- (i) TGYX₁X₂X₃X₄X₅QSPEKSLEWIG (SEQ ID NO:11)
wherein X₁ is Met, Ala or Val; X₂ is Gln, Asp, Glu or Arg; X₃ is Trp or Ala; X₄ is Val or Ser; and X₅ is Lys, Glu or Ala;
- (ii) EINPSTGGX₆X₇X₈X₉X₁₀X₁₁X₁₂KAKAT (SEQ ID NO:12)
wherein X₆ and X₇ are each Thr, Val or Ala; X₈ is Tyr or Phe; X₉ is Asn or Asp; X₁₀ is Gln or Glu; X₁₁ is Lys or Glu, and X₁₂ is Phe or Tyr;
- (iii) YYCARX₁₃X₁₄X₁₅X₁₆PYAX₁₇X₁₈YWGQGS (SEQ ID NO:13)
wherein X₁₃ is Phe, Thr or Gly; X₁₄ is Leu, Ala or Ser; X₁₅ is Trp or Ala; X₁₆ is Glu or Lys; X₁₇ is Met or Ala, and X₁₈ is Asp, Lys or Ser;
- (iv) GYNX₁₉X₂₀X₂₁X₂₂X₂₃X₂₄SHGX₂₅X₂₆LEWIG (SEQ ID NO:14)
wherein X₁₉ is Met or Ala; X₂₀ is Asn, Asp or Arg; X₂₁ is Trp or Ala; X₂₂ is Val or Ser; X₂₃ is Lys or Glu; X₂₄ is Gln or Ala; X₂₅ is Lys or Glu, and X₂₆ is Ser or Ala;
- (v) YYCARX₂₇X₂₈X₂₉YGX₃₀X₃₁X₃₂GQTL (SEQ ID NO:15)
wherein X₂₇ is Ser or Phe; X₂₈ is Gly or Ala; X₂₉ is Arg, Ala or Glu; X₃₀ is Asn or Asp; X₃₁ is Tyr or Phe, and X₃₂ is Trp, His or Ala;
- (vi) X₃₃YYWSWIX₃₄QX₃₅PX₃₆X₃₇GX₃₈EWIG (SEQ ID NO:16)
wherein X₃₃ is Gly or Thr Gly; X₃₄ is Arg or Lys; X₃₅ is Pro or Ser; X₃₆ is Gly or Glu; X₃₇ is Lys or Asp; and X₃₈ is Glu, Leu or Ser;
- (vii)YYCARX₃₉LLX₄₀X₄₁X₄₂X₄₃X₄₄DVDYX₄₅GX₄₆DV (SEQ ID NO:17)
wherein X₃₉ is Gly or Phe; X₄₀ is Arg or Ala; X₄₁ is Gly or Ala; X₄₂ is Gly or Ala; X₄₃ is Trp or Ala; X₄₄ is Asn or Ala; X₄₅ is Tyr or Trp; X₄₆ is Met or Gln;
- (viii) FSGYYWS (SEQ ID NO:8);

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(ix) EINHSGSTNYKTSLSKS (SEQ ID NO:9); or

(x) GLLRGGWNDVDYYYGMDV (SEQ ID NO:10), or

c) a peptide comprising consecutive amino acids having a sequence of any of a) and b), or at least two of the sequences in (a)(i), (a)(ii) and (b)(i) through (b)(x), or

d) a peptide comprising consecutive amino acids having a sequence comprising at least two identical sequences included in (a)(i), (a)(ii) and (b)(i) through (b)(x); and

a solubility enhancer selected from the group consisting of dimethyl-acetamide, polyethylene glycol, polyoxylated castor oil, N-methyl-2-pyrrolidinone, 1-ethenyl-2-pyrrolidinone, polyoxyethylene sorbitan esters, and a substituted β -cyclodextrin.

26. (Canceled)

27. (Currently Amended) A process of lyophilizing the pharmaceutical composition of ~~any one of claims 1-13,~~ claim 1, comprising the steps of:

a) lowering the temperature of the pharmaceutical composition to -40°C ;

b) holding the temperature at -40°C for a predetermined time;

c) raising the temperature of the solution to 20°C ;

d) holding the temperature at 20°C for a predetermined time; and

e) reducing the pressure and holding the temperature at 20°C for a predetermined time, thereby lyophilizing the pharmaceutical composition.

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Claims 28-35. (Canceled)

36. (Original) The process of claim 27, wherein
- step a) is performed within 2 hours;
 - step b) is performed within 3 hours;
 - step c) is performed over 13 hours and at a pressure of 110 μ bar;
 - step d) is performed over 13 hours and at a pressure of 110 μ bar; and
 - step e) is performed over 5 hours and the pressure is reduced to 10 μ bar.

37. (Currently Amended) A lyophilized pharmaceutical composition prepared by the process of ~~any one of claims 27-36~~ claim 27.

38. (Currently Amended) A process of lyophilizing the pharmaceutical composition of ~~any one of claims 1-13,~~ claim 1, comprising the steps of:
- a) lowering the temperature of the pharmaceutical composition to -45°C;
 - b) holding the temperature at -45°C for a predetermined time;
 - c) raising the temperature of the solution to -20°C;
 - d) raising the temperature of the solution to 25°C; and
 - e) holding the temperature at 25°C for a predetermined time, thereby lyophilizing the pharmaceutical composition.

Claims 39-46. (Canceled)

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47. (Original) The process of claim 38, wherein
step a) is performed within 6 hours;
step b) is performed within 3 hours;
step c) is performed over 19 hours and at a
pressure of 150µbar;
step d) is performed over 13 hours and at a
pressure of 150µbar; and
step e) is performed over 8 hours and at a
pressure of 150µbar.

48. (Currently Amended) A lyophilized pharmaceutical
composition prepared by the process of ~~any one of claims~~
~~38-47~~ claim 38.

Claims 49-51. (Canceled)

52. (Original) A packaged pharmaceutical composition
comprised of:
a packaging material; and
a predetermined amount of the lyophilized pharmaceutical
composition of claim 37 or 48.